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SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,304	ROTHSCHILD ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10,19-23,25-37 and 40* is/are pending in the application.

4a) Of the above claim(s) *25-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-10, 19-23, 29-37, and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is written in response to applicant's correspondence filed 1/16/07. Claims 1, 5, 6, 7, 8, 9, 10, 19, 20, 21, 22, 23, 25-37, and 40 are pending. Claims 25-28 are withdrawn from prosecution. Applicant's amendments and arguments have been carefully considered but are not persuasive to place the claims in condition for allowance for the reasons set forth in this office action. **This action is final.**

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s):

A new paper copy of the sequence listing with three additional sequences was filed 1/16/07. However, a new computer readable form was not filed.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, as necessary, a new CRF and a new letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 5-10, 19, 20-23 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The previously set forth 112 2nd paragraph rejection is overcome in view of the amendments to the claim and in view of applicant's remarks on page 15 of the response. A new rejection is set forth for claim 1 and the claims that depend from claim 1.

Claim 1 is indefinite over the recitation "said phenotype" in the last line of the claim because the claim does not previously recite a single phenotype (the recitation of a phenotype was deleted by amendment) and it is not clear what phenotype applicant intends to refer to as "said phenotype." Furthermore, the claim is unclear because it does not set forth how the polymorphism is related to any phenotype or trait. The claim sets forth that it is directed towards identifying pigs to determine "desired meat quality characteristics" yet the body of the claim never sets forth how desired characteristics are identified. The claim sets forth assaying for the presence of the polymorphism but does not set forth how the assaying or the results of the assaying are related to desired meat quality characteristics. The claim does not connect the obtaining, assaying, and relating to the goal of the method, which is to identify pigs with desired meat quality characteristics, and so it is unclear as to how the method steps do or do not accomplish the intended purpose of the method.

Claim 1 is indefinite over the recitation "the presence of a polymorphism in a MC4R gene as set forth in SEQ ID NO: 1" because it is not clear if "as set forth in SEQ ID NO: 1" is meant to modify the "a polymorphism" or if it is meant to modify the MC4R gene. If it is the latter, it is further indefinite because it suggests that SEQ ID NO: 1 provides an entire MC4R gene when in fact SEQ ID NO: 1 provides only a fragment of the gene.

Claim 19 is indefinite, because while the instant specification discloses a TaqI polymorphic site present at position 678 of instant SEQ ID NO: 1, this polymorphic site does not

appear that it would be present at position 678 of the DNA amplified using instant SEQ ID NO: 5 and SEQ ID NO: 6. Comparing these primers to instant SEQ ID NO: 1, one can note that instant SEQ ID NO: 1 overlaps with the primer identified in the sequence listing as SEQ ID NO: 5 by only the final five nucleotides of SEQ ID NO: 5. This means that when SEQ ID NO: 5 is used to amplify a portion of the MC4R gene from pigs the polymorphic position referred to by the instant invention would not be present at position 678 in particular, but would be present at a later numbered position if one begins with position 1 being at the beginning of the amplified fragment when SEQ ID NO: 5 is used as a primer. Therefore, it is confusing if applicant intends to refer, in claim 19, to a different polymorphic site than is the subject of most of the discussion of the instant specification, or if the numbering convention used in the claim is wrong in light of the fact that a primer having SEQ ID NO: 5 would amplify a fragment that has 15 nucleotides upstream of the fragment depicted in instant SEQ ID NO: 1. Review and clarification of the claim is required.

Claim 20 is indefinite because the preamble of the claim sets forth a method for identifying "pigs" but the method steps of the claim refer to testing "an animal" and so it is not clear if applicant intends for the claim to be limited by the preamble obtaining a nucleic acid sample from a pig or if applicant intends for the claim to be sufficiently broad so as to encompass the analysis of any species of animal. Claims 21, 22, and 23 are also indefinite over this issue since they depend from claim 20.

Claim 20 conflicts with itself because it requires obtaining a nucleic acid comprising a gene "as set forth in SEQ ID NO: 1 (in line 4 of the claim)" but then sets forth identifying the presence of a substitution at position 678 of SEQ ID NO: 1. Although the claim clearly requires

obtaining a nucleic acid comprising an MC4R gene as set forth in SEQ ID NO: 1, it is confusing because the rest of the claim appears to be directed towards identifying the presence or absence of a substitution within SEQ ID NO: 1. Further, claim 20 is indefinite over the recitation "a nucleotide substitution at position 678 of the MC4R gene as set forth in SEQ ID NO: 1" because it is not clear if "as set forth in SEQ ID NO: 1" is meant to modify the "nucleotide substitution at position 678" or if it is meant to modify the MC4R gene. If it is the latter, it is further indefinite because it suggests that SEQ ID NO: 1 provides an entire MC4R gene when in fact SEQ ID NO: 1 provides only a fragment of the gene. Amendment of claim 20 to read, for example, "obtaining a nucleic acid sample from a pig, said sample comprising a MC4R gene and identifying the presence or absence of a Taq I in the MC4R gene, said Taq I resulting from a nucleotide substitution at position 678 of an MC4R fragment comprising SEQ ID NO: 1" would overcome this 112 2nd rejection, though 112 1st paragraph rejections may remain.

Claim 22 refers to a nucleotide that is present at "base 678 of the MC4R gene" and this is indefinite because the number of a nucleotide present at a particular position is entirely dependent on the primers used to amplify the fragment. There is no known "base 678 of the MC4R gene" for all pigs or for all possible MC4R genes. For pigs in particular, the full length coding sequence of the MC4R gene is not disclosed in the specification, so what "the MC4R gene" refers to itself is indefinite. Even still, the number of a position in the gene is entirely arbitrary depending on where one begins counting (in the promoter, at the start ATG, at the beginning of an amplification fragment, etc). Applicant amended the claim to recite that the sample is amplified with instant SEQ ID NO: 5 and SEQ ID NO: 6, but did not correct claim 22 with regard to the recitation "base 678 of the MC4R gene." Further, as noted for claim 19, the

polymorphism that is the subject of the instant invention would not be at position 678 of the nucleic acid amplified by SEQ ID NO: 5 and SEQ ID NO: 6.

Claim 32 is indefinite over the recitation "MC4R gene as set forth in SEQ ID NO: 1" because it suggests that SEQ ID NO: 1 provides an entire MC4R gene when in fact SEQ ID NO: 1 provides only a fragment of the gene. Amendment of the claim to recite "MC4R gene fragment as set forth in SEQ ID NO: 1" would overcome this rejection.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-10, 19-23, 29-37, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a pig which possesses a genotype indicative increased pH, decreased Minolta, decreased drip loss, or increased rate of weight gain, wherein a pig homozygous for adenine at position 678 of SEQ ID NO: 1 is indicative of said pig being more likely to have the phenotype than a pig with a guanine at position 678 of SEQ ID NO: 1, said method comprising detecting the nucleotide present at position 678 of SEQ ID NO: 1, and relating the nucleotide to the phenotype, does not reasonably provide enablement for methods which screen other species of animals, or methods which utilize drawn conclusions based on nucleotide(s) present at positions other than 678 of SEQ ID NO: 1, or methods which identify pigs that would produce meat with any other relative meat qualities or methods which identify/screen for any animal having any possible phenotypic trait, particularly, the specification is not enabling for the detection of pigs that would produce meat with

differential marbling based on the nucleotide present at position 678 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Each of the rejected claims are broadly drawn to include at least one of the following: methods for screening any animal (claim 20 in light of the 112 2nd), methods for using polymorphisms in the MC4R gene other than the polymorphism at position 678 of SEQ ID NO: 1 (claims 29, 30, 32, and 37 which recite "a nucleotide substitution at position 678 of SEQ ID NO: 1 but do not limit the nature of the substitution), or methods for using polymorphisms which are "linked" to the instantly disclosed polymorphism (claims 1, 5, 6-8,19, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 40 which recite simply assaying to determine the allele without limiting the assay means).

The specification teaches the use of primers (instant SEQ ID NO: 5 and SEQ ID NO: 6, as identified in the sequence listing) to amplify a portion of the porcine MC4R gene, and that the product size from the PCR is approximately 750 nucleotides (p. 13-14). Subsequent to digestion with the restriction enzyme TaqI, applicant reports the identification of two alleles: allele 1 having bands of about 466, 225, and 76 nucleotides and allele 2 having bands of 542 and 225 base pairs (p. 14). The specification teaches that the polymorphism results from a G→A transition at position 678 of SEQ ID NO: 1, and that the polymorphism results in a missense mutation in the encoded porcine polypeptide from aspartic acid codon to asparagines codon at position 298 of the MC4R protein (p. 15, 1st paragraph). Instant SEQ ID NO: 1 does not appear to be a full length coding sequence for the MC4R receptor since it does not contain the full sequence that would align with the human receptor (see Figures 2 and 3).

The specification makes reference to three markers which are significantly linked to the disclosed porcine polymorphism, markers referred to as SO331, BHT0433, and SO313 (p. 15-16). The specification does not, however provide any discussion of the structure of these markers, which alleles are indicative of what trait, or how to use these particular markers in the claimed assay. MPEP 608.01 (p)[R-2] teaches that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." For claims which rely on "linked markers" and specifically claim 31 which mentions these markers in particular, the guidance in the specification is not sufficient to use these markers in any assay for detection of traits in pigs, or any other animals.

The specification further provide data which demonstrate that pigs homozygous for adenine at position 678 of SEQ ID NO: 1, on average, produce meat that has increased pH, decreased Minolta, decreased drip loss, or increased rate of weight gain relative to pigs with a guanine at that position (see Table 2, page 23). Based on these data, it is reasonable to conclude, for pigs, that the identification of the nucleotide present at this position in the porcine gene is indicative these traits when a homozygous result for the "A" allele is identified.

No significant association is demonstrated between the presence of the polymorphism and marbling in meat from pigs (see Table 2, page 23). Thus, a claim which specifically recites that the polymorphism is indicative of a favorable meat quality, specifically having favorable marbling are not supported by the findings provided in the instant specification. No such claim is currently pendign. Furthermore, based on the data presented in the instant specification it is

highly unpredictable as to whether this specific trait is in fact associated with the presence of the polymorphism. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion. Because applicant's attempt to associate the disclosed polymorphism in pigs with the trait of marbling resulted in a p value of 0.42, it is not possible to conclude that a reliable association exists between marbling and the presence of a particular allele at the identified polymorphic site.

The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

The prior art demonstrates that this mutation is associated with animal fat content, growth rate and feed consumption (WO 00/06777). The prior art is silent with respect to other possible polymorphisms in the MC4R gene or with respect to the association of this particular polymorphism with favorable meat qualities in any other meat producing animal. Neither the specification nor the prior art provide evidence of any universal correlation between MC4R and meat quality in all animals which would conclusively associate the polymorphism instantly disclosed with favorable meat quality in any other animal. Furthermore, the prior art does not provide any evidence that this particular polymorphism is associated with all measures of meat quality.

With regard to the claims that are broadly drawn to testing any animal for any phenotype associated with polymorphism in the MC4R gene, the art supports the fact that it is highly unpredictable which polymorphisms within the MC4R gene will be associated with which phenotypes. For example, Gotoda *et al.* were unable to establish a relationship between a polymorphism in the human MC4R gene and any phenotype (Diabetologica, 1007). Furthermore, the neither the prior art nor the instant specification provide even the sequence of the MC4R protein or nucleic acid encoding the protein for any other traditional "meat" producing species of animal (such as cows, sheep, chicken, fish, etc.).

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is unpredictable whether any additional polymorphisms exist in the porcine MC4R gene, or whether the instantly disclosed polymorphism is present in the genomes of other animals. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield

polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of different species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides pigs. For practice of the claimed invention even within pigs, this is further complicated by the fact that the instant specification provides only a partial sequence of the porcine MC4R gene. Second, after a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with favorable meat quality. Thus, the claimed method of screening animals, for enablement of the full scope, requires the use of unpredictable and potentially non-existent products, and further associations between these products and phenotypes. In this case, the genus is itself undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with favorable meat quality.

Furthermore, it is entirely unpredictable whether or not the MC4R genes of any other organisms contain a SNP at a position homologous to that described in the instant specification for the porcine MC4R gene, whether such a polymorphism would effect a TaqI site, and whether or not such a polymorphism would be indicative of any phenotypic traits. The unpredictability of the interspecies conservation of polymorphic sites is demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that some positions that are polymorphic in the human gene are not polymorphic in other non-primate animals, and vice versa (p.18950, Fig 1).

The converse line of reasoning demonstrates that just finding a identifying a MC4R gene in an animal other than a pig does not necessarily mean that a polymorphism in the gene will be predictive of meat quality or production traits (as is alleged by the specification). It is possible that an apparent MC4R homolog in a non-pig animal might not be functionally equivalent to the MC4R gene in pigs. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if homologs of the MC4R gene were identified and sequenced in other animals, and even if these new MC4R genes displayed polymorphisms, one would have to perform a large amount of experimentation to determine whether or not these putative polymorphisms would be indicative of any particular traits in the animals.

The amount of direction or guidance presented in the specification and the prior art of only one point mutation in the MC4R gene of one species of animal is minimal, given that just the redundancy of the genetic code of the approximately 350 amino acid protein would allow for several thousand different sequences when conserved or non-conserved mutations are considered, millions of different sequences for the pig MC4R gene may exist which may, or may not, have substantial functional differences or association with the traits of interest herein. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art. Particularly, there is no disclosure of complex polymorphisms including repeat link variance, insertions or deletions in MC4R (as in claim 39) which are also associated with favorable meat quality. In addition, a number of the claims recited that the instantly taught polymorphism, "or a polymorphism linked thereto" is used for the detection of

favorable meat quality. However, the specification has not provided any evidence that polymorphisms linked to this single G→A change are in fact associated with meat quality traits. Such an association is highly unpredictable. There is no evidence in the specification provided that the identified polymorphism is causative of the observed traits. This is a significant absence of evidence, since it is possible that the polymorphism is merely a marker for the causative genotype. In light of the fact that the causative genotype has not been identified, it is unpredictable as to whether or not markers which are linked to the instantly disclosed polymorphism would be informative for the traits of interest herein (for example, as claimed in claims 30 and 31, for example).

The level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), the quantity of experimentation that would be necessary to determine even one additional polymorphism in the pig MC4R gene is substantial since there is no predictability for which sequences exist which code for polymorphisms in pig MC4R genes. Applicants have not disclosed how one would go about detecting polymorphisms associated with the traits of interest herein. Because there is no reason to expect that any additional polymorphism is associated with the production of meat with any favorable quality and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators of these traits would require the rearing and subsequent slaughtering of many, many pigs in order to analyze their meat quality and in order to screen the MC4R gene for informative polymorphisms. There is no evidence, however, of any frequency of significant polymorphisms. Further, even if polymorphisms were detected, the polymorphism may not correlate high meat quality. The instantly disclosed polymorphism may be coincident with and

unrelated to a different, unlinked (on the chromosome) polymorphism such as another MC4R polymorphism or a polymorphism in an undetermined gene that actually determines meat quality. The instantly disclosed polymorphism would not have any meaning or effect, but might appear to influence meat traits due to it's close proximity to some other gene.

Furthermore, the level of unpredictability and the level of experimentation required to expand the instantly disclosed methods to include animals of other species are also quite high. There is no teaching in the specification that the disclosed polymorphism even exists in animals of other species. Since there is not evidence that the disclosed polymorphism is causative of the traits (as discussed above), it is highly unpredictable as to whether the polymorphism would mark the same traits in other animals that are slaughtered for meat. Further, in order to provide such evidence the skilled artisan would be required to undertake extensive studies of the meat quality of hundreds upon hundreds of different individual animals of each of many different species of animal. Such experimentation would be inventive in itself.

Due to the broad nature of the claims, the presence of only one working example, the extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

6. Claims 1, 5, 6-8, 19, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods comprising the analysis of nucleic acid sequences from animals wherein the nucleic acid sequences are associated with phenotypes or meat quality traits. The claims are thus broadly drawn to methods comprising the analysis nucleic acids that are indicative of these phenotypes and encompass the use of a multitude of different nucleic acid molecules of a wide variety of unique sequences.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of a large number of nucleic acids comprising a wide variety of nucleic acid sequences. Each of the rejected claims encompasses at least one of the following: analyzing polymorphic sequences from any possible species of animal (claim 20 in light of the 112 2nd) and/or analyzing porcine polymorphic regions other than the single disclosed point mutation at position 678 of instant SEQ ID NO: 1. Some claims require only that the detected polymorphism effect a TaqI restriction enzyme digestion pattern, such a polymorphism could be any substitution (of any length or nucleotide identity) of a sequence element to either create or destroy a TaqI site at position 678 of SEQ ID NO: 1. The rejected claims do not clearly define the nucleotide sequence information or structural limitations regarding what is considered a genotype or polymorphisms that is inherently associated with the traits. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses a partial nucleic acid sequence

a porcine MC4R gene (instant SEQ ID NO: 1). The specification also teaches an analysis of a single polymorphism in this gene, with the polymorphic site begin located at position 678 of SEQ ID NO: 1. The instant specification does not disclose any sequences from any animals other than pig, and does not provide any polymorphisms other than the aforementioned polymorphisms as associated with any particular meat characteristic or phenotype in general. The specification does not provide any other sequences encode "an amino acid position analogous to position 298 of human MC4R."

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other than nucleotide sequence or position within a particular gene), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the specification provides general information about methods to identify particular polymorphisms, and guidance as to how to genotype an animal once a polymorphism has been identified and a correlation to a particular trait has been established, there is no guidance as to how one may *a priori* identify a genotype or polymorphism that is inherently associated with meat quality or other phenotypes.

In the instant application, the provided information regarding specific sequences and genotypes comprising particular polymorphisms used in the examples of the specification do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the sequences, genotypes and polymorphic variants encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a statement that polymorphisms with a particular functionality or association are part of the

invention and reference to a potential method for their identification. The particular nucleic acid sequences are themselves required.

In conclusion, the limited information provided regarding portions of the pig MC4R as provided in the examples of the instant specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for screening any animal for meat quality phenotypes or other general "phenotypes" using polymorphisms in the MC4R gene, or the TaqI restriction pattern of a PCR amplification.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1, 5-10, 19, 30, 31, 35, 36, 37, and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Rothschild *et al.* (WO 00/06777).

Rothschild *et al.* teach a method of identifying an animal which possesses a genotype indicative of a phenotypic trait which comprises obtaining a nucleic acid sample from said animal, assaying for the presence of a polymorphism in the MC4R gene of the sample said polymorphisms being one which has been previously shown to be significantly associated with a phenotypic trait, said polymorphism further being an aspartic acid codon which is changed to an

asparagine codon at an amino acid analogous to amino acid 298 of the human MC4R gene, and associating said animal with said phenotypic trait based upon the genotype present in said animal. Further, Rothschild *et al.* teach a method for identifying a pig which possesses a genotype indicative of increased fat content, said method comprising obtaining a nucleic acid sample from said animal and assaying for the presence of a G → A polymorphism at position 678 of instant SEQ ID NO: 1 (the MC4R gene) (p. 4, lines 14-25). This polymorphism results in a change in the codon which encodes the amino acid at position the position in the pig MC4R gene anaglous to position 298 of the human gene, the polymorphism being either the aspartic acid codon or the asparagine codon. Rothschild et al. teach that animals homozygous for allele 1 had on average less back fat than those homozygous for allele 2 (p. 22), so they relate the polymorphism to a phenotype. The rejected claims require that the polymorphism is "associated with meat quality characteristics of pH, color and drip loss," or that the polymorphism "is correlated with a meat quality trait of pH, color, and drip loss." In the claims, these are statemetns of an inherent property of the polymorphism (whether or not it was disclsoed by Rothschild et al.) but they are not a method limitaitons that clearly distinguish from the method set forth by Rothschild et al. Rothschild et al. complete all of the active process steps set forth in the instantly rejected claims. Rothschild *et al.* teach methods which employ allele specific oligonucleotides (see claim 7, for example), RFLP, PCR amplification and restriction analysis using Taq I (see claims 7-12, for example). Rothschild et al. teach amplificaiton with primers having instant SEQ ID NO: 5 and SEQ ID NO: 6 and that a polymorphism is found at position 678 (p. 10-11). Rothschild et al. teach using markers linked to the polymorphism such as S0331,

BHT0433 and S0313 (see their clms 29-30, for example). The teachings of Rothschild *et al.* meet the limitations of all of the instant claims.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1, 5-10, 19, 20-23, 29, 32-37, and 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6803190.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the issued patent anticipate the instantly claimed invention. For example, claim 1 of the issued patent anticipates instant claims 1, 20, 24, 29, 32, 33, 34, 36, and 40, claim 3 of the issued patent anticipates instant claim 5, claim 7 of the issued patent anticipates instant claim 6, claim 4 of the issued patent anticipates instant claim 7, claim 5 of the issued patent anticipates instant claim 8, claim 6 of the issued patent anticipates instant claim 9, claim 7 of the issued patent anticipates instant claim 10, claim 9 of the issued patent anticipates instant claim 19. Further, though the remaining claims are not clearly anticipated by the issued claims, the issued claims render obvious the claimed invention.

For example, regarding claims 21, 35, and 37, the issued patent does not include a step of selecting animals for breeding. However, it would have been prima facie obvious to have further selected the genotyped pigs for breeding based on the presence of the detected polymorphisms. One would have been motivated to do so in order to have provided a means for breeding pigs which have more consistent traits regarding back fat, daily gain, or feed intake.

Regarding claims 22 and 23, the method steps of amplifying and digesting nucleic acid sample are provided in the claims of the issued patent, the size of the restriction fragments would be an inherent property of the fragments amplified in the claims of the issued patent.

11. Claims 1, 5-10, 19, 30, 31, 33, 35, 36, 37, and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 20-23, and 28-32 of copending Application No. 10/834485. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application either anticipate or make obvious the instantly claimed invention.

Regarding instant claim 1, Claim 1 of the copending application teaches a methods which includes a step of identifying a polymorphism within the MC4R gene of a sample from an animal for the purpose of identifying an animal "which possesses a genotype indicative of the metabolic traits of fat content, growth rate, and feed consumption," with claim 2 reciting that the polymorphism is at position 678 or the PCR product of the MC4R gene. The polymorphism detected in the claims of the copending application is the same polymorphism being detected in the instant claims, and therefore the teachings of claim 2 of the copending application anticipate claim 1 of the instant application. Claim 3 if the copending application recites that the animal is a pig. Thus, it would have been prima facie obvious to one of ordinary skill in the art to have performed the method of claim 2 of the copending application with a pig as the subject, and thus the invention of instant claim 4 is prima facie obvious in view of claims 1-3 of the copending application. The claims of the copending application also addressee method limitations such as those set forth in instant claims 5-10, namely in claims 7-11 of the copending application. Later claims teach that the polymorphism can be identified with the restriction enzyme Taq I and teach identifying restriction fragments which are the same size as those recited in instant claims, and also, the claims of the copending application teach methods for selecting animals with desired traits, methods for indirect selection, methods for identifying animals which include calculating the association between an MC4R genotype and a metabolic trait, and selecting animals. It would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by the copending application so as to practiced any of them together, with the particular polymorphism disclosed in those claims for the detection of desired phenotypes as set forth in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

The rejection of claims 33, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, for new matter is WITHDRAWN in view of the amendments to the claims.

The 112 2nd paragraph rejection of claim 19 is maintained. Applicant points to example 1 of the specification. While it is true that the specification teaches on page 15 that a polymorphism was identified at position 678 of the amplification product (p. 15), this is not consistent with the actual sequence data given in the specification. As shown in figure 1, the polymorphic position is indeed at position 678 of SEQ ID NO: 1. However, this is not the entire fragment that would be amplified with SEQ ID NO: 5 and SEQ ID NO: 6 since SEQ ID NO: 5 clearly has nucleotides on it's 5' end that are not at the 5' end of SEQ ID NO: 1. An amplification product produced using these primers would include SEQ ID NO: 5 in its entirety at the 5' end of SEQ ID NO: 1. Instant SEQ ID NO: 1, however overlaps with SEQ ID NO: 5 only by the final five nucleotides of SEQ ID NO: 5. An amplification product produced with SEQ ID NO: 5 would therefore be fifteen nucleotides longer at the 5' end than SEQ ID NO: 1, and the polymorphic position would be fifteen nucleotide further if one begins counting with nucleotide "1" at the 5' most end of the PCR product. The rejection is maintained.

The rejection for claim 22 is maintained as well. Applicants amended claim 22 to indicate that the nucleic acid sample is amplified with primers SEQ ID NO: 5 and SEQ ID NO: 6, but applicants did not amend the recitation "at base 678 of the MC4R gene" nor did applicants

amend the claim to indicate that the position 678 referred to in the claim is position 678 within SEQ ID NO: 1, nor even position 678 of the amplification product. Thus, the claim remains indefinite. Applicant is advised that the polymorphic position would not be at position 678 of an amplification product amplified with SEQ ID NO: 5 and SEQ ID NO: 6, though it is at position 678 of instant SEQ ID NO: 1.

Applicant traverses the enablement rejection.

Applicant generally summarizes teachings in the specification on pages 17 and 18 of the response.

With regard to "linked markers" applicant points out that the specification teaches that by establishing a linkage between alternative DNA markers and DNA markers known to be associated with the MC4R gene it is possible to indirectly select for the polymorphism with these markers. However, as noted in the rejection, there is not sufficient disclosure in the specification to allow one of skill in the art to make and use this aspect of the invention without undue experimentation. Claims 1, 5, 6-8,19, 29, 30, 31, 32, 33, 34, 35, 36, 37, and 40 all encompass the use of indirect methods of detection as each of these claims simply sets forth assaying for the presence of a polymorphism with no further disclosure of the method used. With the exception of claim 33, the claims are sufficiently broad so as to encompass any means for detection, including indirect detection using unidentified "linked" markers. As noted in the rejection, the "specific examples" given in example 3 are not even described in a way to enable their use since the linked markers are identified only by arbitrary names with no structural features given.

Even so, most of the claims are sufficiently broad so as to encompass the use of any possible linked markers, including markers yet to be disclosed or discovered.

All of the pending claims remain sufficiently broad so as to encompass the detection of a single allele having the "A" allele (allele 2) as being related to the "favorable" phenotypes, when the specification shows that it is the presence of the homozygous allele 2 which is associated with the favorable traits (table page 23 of specification). The results in the specification show that for some traits the average for pigs that are heterozygous is identical to pigs that are homozygous for allele 1 (see pH, for example). The difference shown in the table is for pigs that are homozygous for allele 2 versus pigs that carry allele 1. Furthermore, claims 29, 30, 32 and 37 are sufficiently broad so as to encompass the detection of alleles at this position that are not set forth in the specification and have not been identified in pigs. The claims require detecting a "nucleotide substitution" at position 678 of SEQ ID NO: 1, but they do not set forth the identity of the nucleotide. The recitation that the pigs have "a nucleotide substitution" remains sufficiently broad so as to also encompass the addition of more than one nucleotide provided that a minimal single nucleotide has been substituted.

Claim 20 has been amended in the preamble to set forth that it is a method for identifying pigs, but the method steps of the claims refer only to testing "an animal." The preamble does not clearly limit the method steps which do not refer to pigs in particular but to animals, and so this claim remains problematic for this reason as well.

The rejection under scope of enablement is maintained.

The written description rejection is maintained. While applicant is correct that each of the claims recites assaying for a polymorphism at position 678, applicant does not require directly detecting the polymorphism, and so the claims still encompass indirect selection means that could use any number of nucleic acid markers that have not been disclosed or described. The rejection is maintained.

Applicant traverses the 102(a) rejection pointing to the amendment of the claims to recite "meat quality trait of pH, color, and drip loss." However, as noted in the amended rejection, these additions do not provide method limitations to the claims, they only describe what is an inherent property of the methods taught by Rothschild et al., namely that the polymorphism is associated with the traits whether Rothschild et al. recognized it or not. If applicant wishes to distinguish the methods of the claimed invention from the prior disclosure of Rothschild et al., the actual method steps must incorporate the newly discovered relationship between the polymorphism and phenotype. The rejection is maintained.

To traverse the double patenting rejection, applicant also points to the amendment of the claims to recite "meat quality trait of pH, color, and drip loss." This is not persuasive for the double patenting rejections for the same reasons it was not persuasive for the 102(a) rejection. The rejection is maintained.

The following is an exemplary allowable claim:

A method for identifying a pig which possesses a genotype indicative of the phenotypes increased pH, decreased Minolta, decreased drip loss, and increased rate of weight gain, wherein

a pig homozygous for adenine at position 678 of SEQ ID NO: 1 is indicative of said pig being more likely to have one or more of the phenotypes than a pig with a guanine at position 678 of SEQ ID NO: 1, wherein the increase or decrease is relative to a pig having guanine at position 678 of SEQ ID NO: 1, said method comprising directly detecting the nucleotide present at position 678 of SEQ ID NO: 1 in both alleles of the pig's MC4R gene to determine the pig's genotype, and relating the genotype to the phenotype.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

March 22, 2007